International Journal of Pharmaceutics, 47 (1988) 89–93
Elsevier

IJP 01583

Bioavailability of phenylpropanolamine HCl from tablet dosage forms containing croscarmellose sodium

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(Received 30 September 1987)
(Modified version received 7 March 1988)
(Accepted 4 April 1988)

Key words: Croscarmellose; Drug–excipient interaction; Bioavailability

Summary

A comparative bioavailability study was utilized to investigate the physiological significance of the in vitro drug–excipient interaction between croscarmellose sodium NF and weakly basic drugs. Three formulations of lactose-based tablets containing a 25 mg dose of phenylpropanolamine HCl (PPA), and compressed to comparable hardness, were used: tablet with no disintegrant (CONTROL); tablet with 10% starch (STARCH); tablet with 10% croscarmellose sodium (CROS). Cumulative urinary excretion for 6 healthy subjects in a cross-over study was examined to determine if the drug-excipient interaction resulted in decreased availability. Even though an in vitro dissolution test in distilled water resulted in 40% drug bound for the CROS tablets, no significant differences ($F_{2,15} = 0.237$) in average cumulative amount of drug excreted in the urine after 24 h were found among the 3 dosage forms: CONTROL, 22.94 mg; STARCH, 22.41 mg; CROS, 22.85 mg.

Introduction

A drug–excipient interaction involving weakly basic drugs and croscarmellose sodium NF in aqueous dispersion has been well documented (Chien et al., 1981; Hollenbeck et al., 1983). The interaction exists in vitro under conditions where the cationic form of the drug exists and can exchange with sodium ions associated with the insoluble dispersed croscarmellose (cross-linked sodium carboxymethyl cellulose). In a dispersion where there is an appreciable concentration of smaller cations the drug does not favorably compete for ion exchange sites; when the pH is 2 or more units below the pK_a of the weakly basic drug, as is usually the case in physiologically relevant dissolution media, the extent of the drug–excipient interaction decreases with decreasing pH and with increasing ionic strength.

In in vitro dissolution tests utilizing a fixed volume of distilled water, the drug–excipient interaction may be extensive enough to account for apparent incomplete drug release from the dosage form. For all practical purposes, the interaction only manifests itself when the dissolution medium is distilled water; the apparent free drug concentration is lowest when the total volume of liquid is low and the quantity of croscarmellose sodium is relatively high. A method for estimating the amount of the non-specific interaction has been presented (Hollenbeck et al., 1983).

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Despite the fact that the interaction does not occur in media with low pH and/or an ionic strength similiar to physiological fluids, dissolution results which seem to indicate incomplete release of drug are at the least disconcerting. In addition, according to official policy in the United States (United States Pharmacopeia XXI) distilled water is the first choice for a dissolution standard, and justification must be provided for an exception from this policy (Grady, 1982). The purpose of this study was to determine the effect of the ion exchange interaction on the availability of a representative weakly basic drug.

Materials and Methods

Dosage forms

Phenylpropanolamine hydrochloride (PPA) was selected as the representative drug. All subsequent expressions of dosage and amount or concentration of drug will be in terms of the hydrochloride salt. The 3 dosage forms used in the study are summarized in Table 1. All ingredients used conformed to USP/NF specifications: PPA (ALPS Pharm. Co., Japan); croscarmellose sodium (Ac-DiSol, FMC Corp., USA); pregelatinized starch (Starch 1500, Colorcon Corp., U.S.A.); lactose (anhydrous, direct tableting, Sheffield Products, U.S.A.); magnesium stearate (Ruger Chemical Co., U.S.A.).

A small-scale manufacturing procedure was used to ensure that the study was not confounded by content or weight variability. A 25 g batch of each tablet formulation was mixed by geometric addition and trituration in a mortar with a pestle. The magnesium stearate was withheld and added at the end with light mixing. Aliquots of 500 mg were hand-weighed and pressed manually on a hydraulic press (Model C, Fred S. Carver Inc., U.S.A.) with sufficient pressure, based on preliminary trials, to obtain a tablet hardness of approximately 35 N. Hardnesses were determined using a commercially available tablet hardness tester (Erweka Model TBH 28, F.R.G.). Weight and hardness data for the 3 treatments are presented in Table 1.

TABLE 1

Formulations and tablet properties for the PPA dosage forms

	Treatment		
	CONTROL (mg)	STARCH (mg)	CROS (mg)
Formulation			
Phenylpropanolamine HCl	25	25	25
Croscarmellose sodium	–	–	50
Pregelatinized starch	–	50	–
Lactose	470	420	420
Magnesium stearate	5	5	5
Target tablet weight	500	500	500
Tablet properties *			
Weight (mg)	496 (3.4)	497 (5.2)	502 (6.4)
Hardness (N)	37.8 (7.9)	32.6 (3.4)	37.0 (1.7)
Apparent content ** (mg)	24.4 (0.37)	24.1 (0.73)	16.2 (0.31)

* Each presented as an average of 5 determinations; S.D.s are included in parentheses.

** Expressed as an average per tablet as determined in distilled water.

Protocol

Six healthy male volunteers were recruited as subjects for the randomized cross-over study. Each subject ingested, on 3 separate occasions within a 3-week period, one of the 3 unidentified drug products. At least 3 days elapsed between treatments.

Subjects did not consume food for an 8 h period prior to dosing. Immediately before administration of the drug product, the participant collected a sample of urine to serve as a blank. Urine samples were scheduled at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 18 h post dosing. All urine was collected for the 24 h post-dosing period. During the 8 h period subsequent to dosing, liquid consumption was restricted to water and a caffeine-free beverage. Standard meals were provided by the investigator and consumed by the participants between the scheduled 6- and 8-h samples. Samples were refrigerated and urine volumes were determined by the analyst at the time of extraction. In no case

did more than 2 days elapse before the extractions were completed.

Extraction procedure

For each sample and blank, a 7.5 ml volume of urine was placed in a glass screw cap culture tube. A 400 μl volume of 0.05% ephedrine hydrochloride (EP) was added as an internal standard. After addition of 100 μl of 5 N aqueous sodium hydroxide solution, approximately 6 ml of HPLC grade ether was added. The tubes were capped and inverted at a rate of approximately 10 times per min for 5 min. The tubes were then centrifuged at 1500 rpm for 1 min to facilitate separation of the immiscible liquids, and placed in a freezer until the aqueous phase was frozen. The ether layer was then decanted into a second culture tube and 1.5 ml of 0.5% phosphoric acid was added. The liquids were mixed by inversion as before, and returned to the freezer. When the aqueous layer was frozen, the ether layer was discarded and after thawing, approximately 1 ml was transferred with a disposable glass pipette to an HPLC vial subsequently sealed with a Teflon-lined rubber closure.

Chromatography

All analyses of urine samples were performed using a high-performance liquid chromatograph (Hewlett Packard Model 1084B). The assay employed was a slight modification of a published assay for determination of PPA in serum and urine (Dowse et al., 1983). The separation was performed using a 10-cm reverse-phase column (Nova Pak C_{18}, Waters Associates) with an aqueous mobile phase containing 20% acetonitrile, 0.005 M heptane sulfonic acid, and 0.002 M monobasic ammonium phosphate. Reagents were of at least HPLC grade. The water used was distilled in glass and the mobile phase was filtered with the aid of vacuum through a 0.45 μm aqueous filter (Type HA, Millipore Corp.). The flow rate was 1.0 ml/min and the solvent and column were maintained at 30 °C. Ephedrine hydrochloride (EP) was used as the internal standard and quantification was accomplished using a variable wavelength UV detector at 220 nm monitored by an internal integrator. The injection volume normally used was 30 μl; in situations where the extraction efficiency was low, repeat injections using a larger volume were used to permit integration of the peaks.

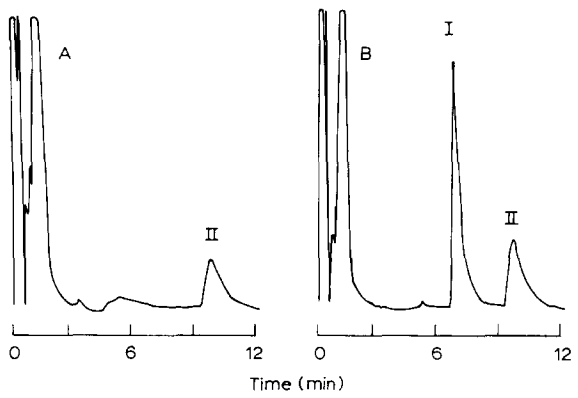

Fig. 1. Representative chromatograms for extractions from blank urine (A) and the 30 min postdosing sample (B). Key: (I) PPA; (II) ephedrine.

Representative chromatograms are presented in Fig. 1. A linear calibration between the PPA/EP peak area ratio and amount of drug injected for spiked urine samples was obtained in the range of 0–375 μg of PPA (slope = 0.00328; intercept = 0.0640; $r^2 = 0.991$). To account for variation in column performance, extractions prepared from spiked urine samples were included in each set of samples analyzed and used as standards for that set of determinations.

Dissolution testing

Dissolution testing was performed using an official testing method (Apparatus 2, United States Pharmacopeia XXI) stirring at 50 rpm with distilled water maintained at 37 °C as the dissolution medium. The multiple spindle apparatus (Hanson Research Corp.) was calibrated with disintegrating and non-disintegrating standards prior to use. Six tablets representing each formulation were examined. Sampling with replacement was done manually at the following elapsed time intervals: 0, 15, 30, 60, and 120 min. Free drug concentration was determined after filtration of the sample through a 5 μm filter needle (Becton Dickinson & Co.) using the HPLC method cited above. In this case, however, no extraction was performed; the internal standard was added and the aqueous solutions were injected directly.

Apparent content, included in Table 1, was determined utilizing the same assay procedure for 5 individual tablets from each formulation by vigorously mixing each tablet in 500 ml of distilled water at room temperature using volumetric glassware.

Results and Discussion

PPA was chosen as a representative drug because it is weakly basic ($pK_a = 9.4$) (Merck Index), it is a safe drug found in many over-the-counter products, it is used at dosage levels high enough to allow for easy and accurate quantification, and approximately 80–90% of the dose is excreted unchanged in the urine (Sinsheimer et al., 1973).

The design of test formulations and appropriate controls was approached with pre-eminent concern about biopharmaceutical implications of the drug–excipient interaction. A larger than necessary tablet (500 mg) with an excessive proportion of croscarmellose (10%) was employed to exaggerate the ultimate drug–excipient interaction in distilled water. Using the rough approximation method presented in the literature (Hollenbeck et al., 1983), assuming a 500 ml volume of distilled water at 25 °C and a resulting pH of 7, 25% of the PPA would be expected to be associated with the disintegrant.

In vitro results

A limited study was done to verify the quality of the dosage forms and substantiate the existence of the drug–excipient interaction. The weight and hardness determinations presented in Table 1 confirm that the small scale manufacturing procedure produced a set of dosage forms unbiased by differences in tablet hardness with little weight variation. The average tablet weight for each group was within 1% of the target weight, and no tablet varied by more than 3% from the group average.

The content determinations were performed in distilled water utilizing volumetric glassware. Each of the tablets used for the content determinations for the CONTROL and STARCH treatments deviated by less than 5% from the target dose of 25.0 mg. The average apparent content of drug for the croscarmellose containing formulations was 16.2 mg, confirming the impact of the drug–excipient interaction. This level corresponds to approximately 33% bound PPA; a value slightly greater than expected from the approximate calculation referred to above, and slightly less than that observed in the dissolution tests.

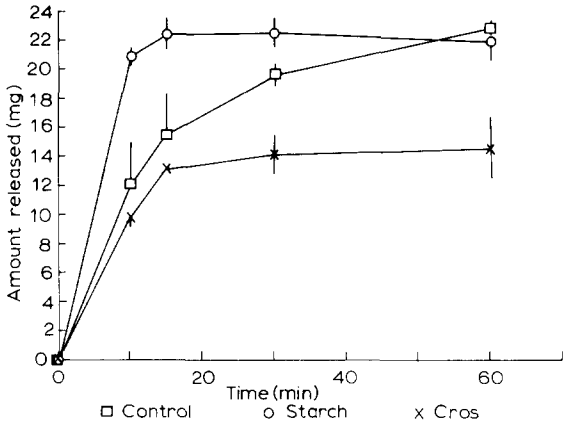

Fig. 2. Dissolution profiles for the control (CONTROL), starch-containing (STARCH), and croscarmellose sodium-containing (CROS) dosage form in distilled water at 37 °C. (Error bars represent ±2 S.D.s from the mean.)

A dissolution profile for each dosage form is presented in Fig. 2. No increase in apparent amount released was observed after 60 minutes. The CONTROL formulation contained a soluble filler but did not include a disintegrant. Release of the drug from the CONTROL lagged slightly behind the STARCH treatment, but both dosage forms presented complete release after 60 min. The tablet dosage form containing croscarmellose sodium presented the profile expected for a dosage form containing a disintegrant that interacts with the drug. The dissolution profile reaches a maximum at essentially the same time as the starch containing dosage form yet the apparent amount released is approximately 60% of that expected.

In vivo results

Presented in Fig. 3 are the cumulative urinary excretion profiles for all subjects given the CONTROL, STARCH, and CROS formulations. The CROS treatment does not appear to be significantly different from either the CONTROL

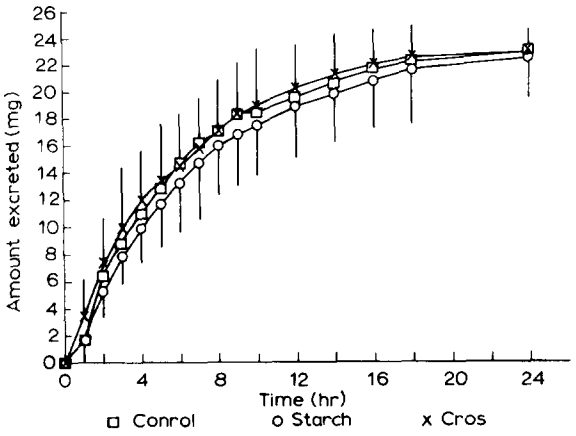

Fig. 3. Average cumulative amounts of PPA excreted in the urine for control (CONTROL), starch-containing (STARCH), and croscarmellose sodium-containing (CROS) dosage forms in all subjects. (Error bars included for the STARCH and CROS treatments represent ± 2 S.D. from the mean.)

and/or STARCH treatment at any time point. An analysis of variance (X-STAT, Wiley Scientific) for the 24 h cumulative amount of PPA excreted in all treatments resulted in an F-ratio of 0.2373. The critical F-values at the 99 and 95% confidence levels with 2 and 15 degrees of freedom are 6.36 and 3.68, respectively. Even the most conservative of tests would not be able to accept the alternate hypothesis that one or more of the means differs from the others.

Conclusion

While a significant drug–excipient interaction between PPA and croscarmellose is observed in vitro in distilled water, this interaction does not adversely influence the bioavailability of PPA from a solid dosage form containing croscarmellose as a disintegrant.

Since the drug–excipient interaction is based on a non-specific ion exchange mechanism, it is reasonable to expect that these results are not specific for PPA. In vitro content determinations and dissolution tests for PPA and other weakly basic drugs in the presence of croscarmellose sodium utilizing dissolution media other than distilled water (eg. 0.1 N HCl, isotonic sodium chloride solution, simulated gastric fluid, or simulated intestinal fluid) present no indication of a drug–excipient interaction (Fan, 1985). A dissolution medium with ionic strength similiar to physiological fluids would therefore seem more appropriate for the testing of dosage forms containing croscarmellose and weakly basic drugs.

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